Pharmacoepidemiological study protocol ER13-9468

A retrospective cohort study to investigate the initiation and persistence of dual antiplatelet treatment after acute coronary syndrome in a Finnish setting – THALIA

Author: Tuire Prami

Protocol number: ER13-9468, ME-CV-1306

Sponsor: AstraZeneca Nordic Baltic

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Study Information

Title	A retrospective cohort study to investigate the initiation and persistence of dual antiplatelet treatment after acute coronary syndrome in a Finnish setting – THALIA
Protocol version identifier	ER13-9468 ME-CV-1306
EU PAS register number	Study registration in ENCePP will be performed after the study protocol approval.
Active substance	ticagrelor (ATC B01AC24), clopidogrel (B01AC04), prasugrel (B01AC22)
Medicinal product	Brilique, Plavix, Clopidogrel accord, Clopidogrel actavis, Clopidogrel krka, Clopidogrel mylan, Clopidogrel orion, Clopidogrel teva pharma, Cloriocard, Efient
Product reference	N/A
Procedure number	N/A
Marketing authorization holder financing the study	AstraZeneca Nordic Baltic: Brilique (ticagrelor)
Joint PASS	No
Research question and objectives	To describe initiation and persistence of dual antiplatelet treatment in invasively or non-invasively treated patients hospitalized for acute coronary syndrome
Country of study	Finland
Author	Tuire Prami

Marketing authorisation holder

Marketing authorization holder	AstraZeneca Nordic Baltic SE-151 85 Södertälje Sweden
MAH contact person	Pål Hasvold

Table of contents

1 List of abbreviations

List of main abbreviations used in the study protocol

ACS	Acute coronary syndrome
ASA	Acetylsalicylic acid
ATC	Anatomical Therapeutic Chemical
DAPT	Dual antiplatelet treatment
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
ICD-10	International classification of diseases, 10th revision
NCSP	NOMESCO classification for surgical procedures
NSTEMI	non-ST elevation myocardial infarction
MI	Myocardial infarction
OAP	oral antiplatelet
PCI	Percutaneous coronary intervention
ID	Patient identification number
SAP	Statistical analysis plan
SID	Study identification number
STEMI	ST elevation myocardial infarction
THL	National Institute for Health and Welfare

2 Responsible parties

Sponsor:	AstraZeneca Nordic Baltic
Study conduct:	EPID Research Oy, Metsänneidonkuja 12, FI-02130 Espoo, Finland
Principal investigator:	Tuire Prami (Ph.D.), EPID Research
Co-investigators:	Pasi Korhonen (Ph.D., Adj. prof. biostatistics), EPID Research
	Fabian Hoti (Ph.D.), EPID Research
Sponsor project lead:	Pål Hasvold (Medical Evidence Scientific Lead), AstraZeneca Nordic Baltic
Steering committee:	1-3 Finnish cardiologist will be named to participate the steering committee.

3 Abstract

Title: A retrospective cohort study to investigate the initiation and persistence of dual antiplatelet treatment after acute coronary syndrome in a Finnish setting – THALIA

Rationale and background: Myocardial infarction affects about 5000 patients in Finland per year. Almost 20% of them die within one year after the event. Dual antiplatelet treatment with low dose acetylsalicylic acid and oral antiplatelet is recommended for patients with acute coronary syndromes. New OAPs have recently been introduced in the market in the Nordic countries.

Research question and objectives: The main objective of this study is to characterize and describe the patients treated with DAPT vs. non-DAPT treated patients, and the switch patterns and discontinuation rates of DAPT treatments.

Study design: Retrospective observational database linkage cohort study

Study setting and population: Patients discharged from hospital following admission for unstable angina pectoris or myocardial infarction in 2009-2013. The patients will be followed-up until moving abroad, death or the end of year 2013, whichever occurs first.

Exposure variables: Use (or non-use) of ticagrelor (ATC code B01AC24), clopidogrel (B01AC04) and prasugrel (B01AC22).

Other covariates: Characterization of e.g. prior cardiovascular history, interventions associated with index event, cardiovascular morbidity during follow-up associated with DAPT medication changes, major co-morbidities and other medications

Data sources: Finnish Hospital Care Register (HILMO) and Social HILMO maintained by the National Institute for Health and Welfare, Prescription Register maintained by the Social Insurance Institution, and Causes of Death Registry maintained by Statistics Finland

Study size: About 25 000 myocardial infarction cases and up to 300 000 hospitalizations due to any type of cardiac attacks

4 Amendments and updates

No.	Date	Section of study protocol	Amendment or update	Reason
1.	none	none	None	none
2.	none	none	None	none

5 Milestones

Milestone	Planned date
Start of data permit process	03/2014
Registration in the ENCePP e-register	03/2014
End of data permit process	08/2014
Start of data collection	08/2014
End of data collection	09/2014
Start of data analysis	09/2014
End of data analysis	12/2014
Start of study reporting process	11/2014
Final report of study results	01/2015
Start of scientific reporting process	01/2015

6 Rationale and background

The prevalence for coronary artery disease is more than 50 000 patients in Finland with almost 70 000 attacks per year (www.sydanliitto.fi/sairastavuus-ja-sairastuvuus, read 06 Feb 2014). According to the PERFECT study performed by the National Institute for Health and Welfare (THL) the incidence of new myocardial infarction (MI) cases was 269 per 100 000 inhabitants in Finland during the years 2008-2010. MI affected then nearly 5000 new patients every year. Of these patients 6.7% died within 7 days and 19% within one year from the MI. Up to 40% of the MI patients were treated with percutaneous coronary intervention (PCI). (www.thl.fi/fi_FI/web/fi/tutkimus/hankkeet/perfect/sydaninfarkti/perusraportit, read 21 Jan 2014) Acute MIs can be divided into three categories according to ST segment elevation: ST elevation myocardial infarction (STEMI), non-ST elevation myocardial infarction (NSTEMI) and unspecified MIs. Corresponding ICD-10 code groups are I21.0-I21.3, I21.4 and I21.9, respectively.

MIs resulting from atherosclerotic plaque rupture with subsequent thrombosis lead to complete or near complete occlusion of an epicardial coronary artery [1]. Minimization of the mechanical obstruction from thrombus is the main goal of therapy in ST elevation myocardial infarction. Recurrent ischemic events are still quite frequent after MI, while sudden cardiac death is less common [2]. However, the incidence of these events has declined over time that supports the notion that contemporary treatments effectively improve outcomes after MI.

Dual antiplatelet treatment (DAPT) with low dose acetylsalicylic acid and oral antiplatelet (OAP) is recommended for patients with acute coronary syndromes (ACS) whether treated invasively or non-invasively. Guidelines recommend DAPT inhibition to be maintained up to over 12 months unless contraindications are present, such as a high risk of bleeding (In Finland: Current Care Summary for STEMI, 2011, and Current Care Summary for Coronary event: unstable angina pectoris and cardiac infarction without ST elevation, 2009, both available online at www.kaypahoito.fi, read 05 Feb 2014).

New OAPs have recently been introduced in the market for treatment of ACS patients in the Nordic countries Denmark, Finland, Norway and Sweden.

How these multiple DAPT treatment options are used in real life clinical practice is not known regarding:

- Patient selection for different DAPT treatments and no DAPT treatment
- Persistence of OAP treatments
- Switch pattern of OAP treatments
- Patient adherence to OAP treatments

7 Research questions and objectives

The objective of this study is to characterize and describe:

- Patients treated with DAPT vs. non-DAPT treated patients
- Patients treated with different DAPT treatments
    - Proportion of patients completing 3, 6, 9 and 12 months treatment
- Switch patterns for DAPT treatments
- Discontinuation rates of DAPT treatments
- Medication possession rate of DAPT treatments

8 Research methods

8.1 Study design

This is a retrospective observational database linkage cohort study using patient level data from different nationwide registers in Finland.

8.2 Setting and population

Study population consist of patients discharged alive from Finnish hospitals following admission for unstable angina pectoris (ICD-10: I20.0) or myocardial infarction (I21-I24) between 01 Jan 2009 and 31 Dec 2013. The discharge day is called index date. The patients will be followed-up from the index date until moving abroad, death or the end of year 2013, whichever occurs first. Medical history is taken into account for five years before the index date.

8.3 Variables

Exposure definitions:

Due to the lack of information on acetylsalicylic acid (ASA) purchases in the nationwide registers (see 8.9 for more details) the assumption of DAPT use is based on OAP use. OAPs of interest are ticagrelor (ATC code B01AC24), clopidogrel (B01AC04) and prasugrel (B01AC22). Ticagrelor has been on the Finnish market since 2010 but the reimbursement status was given in 2012. For prasugrel we have data since 2010 and for clopidogrel for the whole study period since for it the marketing authorization was given already in 1998.

A patient is defined to receive DAPT for unstable angina pectoris or myocardial infarction if a ticagrelor, clopidogrel or prasugrel prescription is filled after the discharge from hospital. The duration of the medication is based on the number of purchased tablets since after the initiation dose (given in hospital) the daily dosing is uniform for all patients: 2 tablets of ticagrelor (90 mg), 1 tablet of clopidogrel (75 mg) and 1 tablet of prasugrel (5 mg or 10 mg but not varying).

Variables for patient characterization:

- Age
- Gender
- Prior cardiovascular history
    - ICD-10 diagnoses
    - Special reimbursement statuses
    - Prior interventions
        - Interventions with a NCSP (NOMESCO classification for surgical procedures) code beginning with FN (coronary arteries)
- Interventions associated with index event
    - Interventions with a NCSP code beginning with FN
- Cardiovascular morbidity during follow-up associated with prolongation, switch or discontinuation of DAPT treatment
    - ICD-10 diagnoses
    - Interventions with a NCSP code beginning with FN
- Major co-morbidities
    - ICD-10 diagnoses

- Special reimbursement statuses

- Other medications
- Type of hospital:
  - Local hospital
  - Central hospital
  - University hospital

8.4 Data sources

Registers used in the study and the relative register holders are presented in Table 1.

Table 1. Registers used in the study with the register holders and relevant register contents

Register	Register holder	Content
Finnish Hospital Care Register (HILMO)	National Institute for Health and Welfare	Diagnoses (incl. cancers *) Interventions Hospitalization periods
Social HILMO	National Institute for Health and Welfare	Institutionalization (other than hospitalization) periods
Prescription Register	Social Insurance Institution	Drug purchases Special reimbursements Place of domicile **
Causes of Death Registry	Statistics Finland	Time and causes of death

* The study will not include separate cancer registry

** For taking moving abroad during the follow-up period into account.

The variables related to different registers are listed in Annex 2.

Data permit process and data linkage:

Approval of Ethical Review Board of Hospital District of Helsinki and Uusimaa (HUS) will be requested to cover the nationwide study. Data permits will be requested from each registry holder based on the study protocol and ethical approval. If the ethical approval is not received EPID Research will not proceed with the permit process, and the study is considered to be ceased. Neither can the study be completed if one of the register holders dismisses a permit application.

Patients with unstable angina pectoris or myocardial infarction between 01 Jan 2009 and 31 Dec 2013 are identified by The National Institute for Health and Welfare (THL). THL will then convert the patient identification numbers (IDs) to study IDs (SIDs) and send the IDs and the SIDs to other register holders: Social Insurance Institution and Statistics Finland. All the three register holders will then mine the study data based

on the variable lists presented in the Annex 2 and send the raw data to EPID Research without IDs (including SIDs only). EPID Research will be the register holder for the study database also in the responsibility of destroying the data after the study.

8.5 Study size

In Finland there are approximately 5000 new MI cases every year meaning 25 000 cases during the study period. In total we may find up to 300 000 hospitalizations due to any type of cardiac attacks.

Based on the number of patient receiving reimbursement for OAP purchases (open access data available for years 2010-2012: www.kela.fi/kelasto, read 06 Feb 2014) during the study period there have been approximately 150 000 clopidogrel users (during the years 2009-2013), 2000 prasugrel users (2010-2013) and 1500 ticagrelor users (2012-2013). For clopidogrel there are also other indications than the ones of interest (such as stroke). However, at least about 150 000 of the cardiac patients included in the study would be untreated with OAPs.

8.6 Data management

R language (http://www.r-project.org) will be used for in data management for creating the analysis database and in statistical analysis for creating tabulations and graphics as well as in all statistical modeling. R language is described more detailed in report "R: Regulatory Compliance and Validation Issues: A Guidance Document for the Use of R in Regulated Clinical Trial Environments" (www.r-project.org/doc/R-FDA.pdf, read 07 Feb 2014). Full audit trail starting from raw data obtained from register holders, and ending to statistical tables and graphs in reports will be maintained. Source code of data management and data analyses is kept for inspection for five years after publication of results. The study may be inspected by the sponsor's independent representative(s), steering committee, or by the competent authorities.

All study data and supporting documents will be retained for five years after the end of the study and then destroyed. As the register holder of the study register EPID Research is in charge of archiving and deleting the data. Secure archives will be maintained for the orderly storage and retrieval of all study related material. An index shall be prepared to identify the archived contents and their location. Access to the archives will be controlled and limited to authorised personnel only. Access to the study data cannot be given to any third parties, neither the study data can be used to other purposes than prescribed in this protocol. All requests to use the study data for other purposes than mentioned in this study protocol must be subjected to appropriate data permit processes.

8.7 Data analysis

The planned analyses are presented shortly in this chapter. A more detailed plan will be prepared in a separate statistical analysis plan (SAP).

Drug treatment patterns in the study populations will be described as:

1. Proportion of patients with OAP medication.
    - Time from index date to start of medication will be described.
    - Persistence for the first drug usage period after index date will be presented using Kaplan-Meier plots (see SAP).
2. Proportion of patients treated with different OAPs (any OAP and specific OAPs) for 3 months, 6 months, 9 months or 12 months after index day.

- 3 months treatment equals to 84 tablets of clopidogrel/prasugrel and 168 tablets of ticagrelor.
- Treatment gaps up to 7 days are included as treatment time in a continuous treatment period.
- Treatment periods with gaps of 8-30 days are considered as continuous treatment. However, exposure time is adjusted to exclude the exposure gaps.
    - If a gap in drug exposure occurs during a hospitalization period and the drug exposure continues after discharge the gap is ignored.
    - If the start of a gap in drug exposure occurs at time of institutionalization it is assumed that drug exposure continues during institutionalization.
- Cardiovascular morbidity during follow-up associated with OAP medication prolongation will be described.

3. Switch patterns of OAP medication.
    - Switch is defined as purchase of another OAP than the initial OAP.
    - Time to switch will be described.
        - Separate descriptions will be performed for the patient group with at least 12 months of follow-up information.
        - Separate descriptions will be performed for the patient group with less than 30 days of original OAP use before the switch.
    - Type of switch will be described:
        - clopidogrel – prasugrel
        - clopidogrel – ticagrelor
        - prasugrel – clopidogrel
        - prasugrel – ticagrelor
        - ticagrelor – clopidogrel
        - ticagrelor – prasugrel
    - Also the switch from non-DAPT medication to DAPT medication (OAP starting later than within 30 days from the index date) will be described.
    - Cardiovascular morbidity during follow-up associated with OAP medication switch will be described.
4. Discontinuation rates and switch patterns of OAP medication within 12 months after index day.
    - Discontinuation is defined as more than 30 days treatment gap (after the last day of medication).
    - In case of a restart of OAP treatment after a > 30 days treatment gap the data will be analysed separately from the original treatment period.
    - If a gap in drug exposure occurs during a hospitalization period and the drug exposure continues after discharge the gap is ignored.

- If the start of a gap in drug exposure occurs at time of institutionalization it is assumed that drug exposure continues during institutionalization.
- Cardiovascular morbidity during follow-up associated with OAP medication discontinuation will be described.

5. Medication possession rate.
   - Number of treatment days (= 1 tablet per day for clopidogrel and prasugrel; 2 tablets per day for ticagrelor) based on tablet purchases during the observation period (from index day to the last day of medication) divided by the number of days in the observational period * 100.
     - If a gap in drug exposure occurs during a hospitalization period and the drug exposure continues after discharge the gap is ignored.
     - If the start of a gap in drug exposure occurs at time of institutionalization it is assumed that drug exposure continues during institutionalization.

The study patients will be characterized in terms of:

- Age
  - Continuous (years)
  - Categorical (< 50, 50-64, 65-74, 75-84, ≥ 85 years)
- Gender
- Time spent in the hospital before discharge at index date
- Prior cardiovascular history within five years before index date
  - e.g. number of prior MIs and type of interventions (see SAP)
  - Both special reimbursement statuses and diagnosed are used (see SAP).
- Interventions associated with the index event (within 30 days before the index event)
  - e.g. PCI performed in association with the index event MI
- Cardiovascular morbidity during follow-up associated with prolongation, switch or discontinuation of DAPT treatment (see SAP)
- Major co-morbidities
  - e.g. number (see SAP)
  - Both main and secondary diagnoses are included.
  - Charlson co-morbidity index score will be calculated as the weighted sum of the presence of a number of co-morbidities (see SAP).
- Other medications
  - e.g. number of concomitant drugs

  - The baseline period for medication is defined from one year prior to index day until the index day. Medications must be ongoing at the time of hospitalization related to the index event.

- Type of hospital:
  - Local hospital
  - Central hospital
  - University hospital
- Calendar year

For baseline description all the patients with index dates in 2009-2013 will be included in the analysis. For follow-up measurements at least one month of follow-up at the end of the study period is needed (Dec 2013).

All continuous variables will be described using standard statistical measures: number of observations, mean, standard deviation, median 1st and 3rd quartile, minimum and maximum. All categorical variables will be summarized with absolute and relative frequencies.

8.8 Quality control

The study will be conducted as specified in this protocol. All revisions to the protocol must be approved by the sponsor, the principal investigator and the co-authors of the study. All changes to the protocol shall be properly documented as protocol amendments and when necessary such protocol amendments are delivered to register holders.

The study protocol has been written by following the Code of Conduct by the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance, ENCePP (www.encepp.eu/code_of_conduct/documents/CodeofConduct_Rev2.pdf). The protocol also follows the key elements of the Guideline for Good Pharmacoepidemiology Practices by International Society for Pharmacoepidemiology (www.pharmacoepi.org/resources/guidelines_08027.cfm) and the Guidance for Industry and FDA Staff "Best Practices for Conducting and Reporting Pharmacoepidemiologic Safety Studies Using Electronic Healthcare Data" (www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM243537.pdf).

The study protocol will be registered in the ENCePP E-register of Studies (www.encepp.eu/encepp/studiesDatabase.jsp). Study results will also be published in ENCePP pages.

About storage of records and archiving of the statistical programming performed to generate the results, and possible audits, see 8.6. Due to the study type (register study using administrative databases) on-site monitoring will not be performed.

8.9 Limitations of the research methods

Primary care data and hospital clinical data (weight, laboratory samples, blood pressure etc.) are not available for this study, thus proper baseline risk cannot be estimated. The cohort entry data request includes ICD-10 codes I20.0 (unstable angina pectoris) and I21-I24 referring to acute myocardial infarction and its complications. The quality of code use of I23-I24 (complications) will be evaluated. The aim is to form the cohort of acute cases only. In general the HILMO data quality is high; more than 95% of discharges can be identified from this nationwide register [3].

Coverage of the Prescription Register containing reimbursement information of all permanent residents of Finland is about 97%. Missing data includes relatively inexpensive packages and over the counter medications that are not reimbursed. Thus fully reliable information on ASA use is not available. DAPT treatment is then defined as OAP use only. For ASA use without OAP we cannot make any estimations.

Medications used during hospitalizations are not available. However, based on the hospital care register the hospitalization periods can be taken into account to define gaps in the drug treatment periods. Also moving abroad or institutionalization during the follow-up period will be taken into account.

9 Protection of human subjects

This is a fully register-based study and patients will not be contacted in any phase of the study. The study does not affect the treatment of the patients.

EPID Research will receive unidentifiable data including SIDs only. Patient data handled by the researchers do not then include IDs that ensures the data protection of the patients. EPID Research employees have undertaken professional secrecy and are aware of 'their' concern with the Act on the Openness of Government Activities 621/1999 (based on which the data can be received from the register holders). The study registers are formed on the basis mentioned in the Personal Data Act (523/1999) §12 and the data is handled as described in §14 therein.

The protocol will be subjected to Ethical Review Board of Hospital District of Helsinki and Uusimaa for review and approval. Register notification of the forming study registers will be sent to the Office of the Data Protection Ombudsman.

10 Management and reporting of adverse events/adverse reactions

This study does not meet the criteria for adverse event reporting.

11 Plans for disseminating and communicating study results

The principal investigator together with the co-investigators will write a study report. This report will be delivered to the sponsor and steering committee. After study report, the principal investigator and co-investigators with co-authors (members of the steering committee and possible other contributors) will prepare (a) scientific manuscript(s) for academic publication. The steering committee decides the publication forums.

An abstract of the study findings will be provided through the ENCePP e-register of studies within three months following the final study report. According to the ENCePP Code of Conduct the principal investigator is responsible of publication of the results. The abstract of the main results of the study will be published, whether positive or negative. In no way shall the interpretation and presentation of the results be aimed towards any commercial, financial or personal interests. The sponsor is entitled to view the final results without unjustifiably delaying the publication.

The primary investigator and AstraZeneca are committed to ensuring that authorship for all publications should comply with the criteria defined by the International Committee of Medical Journal Editors, ICMJE. It is stated that each author should have participated sufficiently in the work to take public responsibility for the content (www.icmje.org/recommendations/browse/roles-and-responsibilities/defining-the-role-of-authors-and-contributors.html, read 18 Mar 2014). AstraZeneca believes that participation solely in the collection of data or drafting the manuscript does not justify authorship. These conditions apply equally to external investigators and to AstraZeneca employees.

12 References

1 Thomas M, Das K, Nanjundappa A, *et al.* Role of thrombectomy in acute myocardial infarction. *Expert Rev Cardiovasc Ther* 2009;7:289–97.

2 Jokhadar M, Jacobsen SJ, Reeder GS, *et al.* Sudden death and recurrent ischemic events after myocardial infarction in the community. *Am J Epidemiol* 2004;159:1040–6.

3 Sund R. Quality of the Finnish Hospital Discharge Register: a systematic review. *Scand J Public Health* 2012;40:505–15.

13 Approvals

We have reviewed this study protocol (ER13-9468, Version 1.0, dated 18 March 2014) and agree to its terms by signing it.

Role	Name	Address	Date	Signature
Principal investigator	Tuire Prami	EPID Research Metsänneidonkuja 12 FI-02130 Espoo	18.3.2014	Tuire Prami
Co-author	Pasi Korhonen	EPID Research Metsänneidonkuja 12 FI-02130 Espoo	18.3.2014	Pasi Korhonen
Co-author	Fabien Hoti	EPID Research Metsänneidonkuja 12 FI-02130 Espoo	18.3.2014	Fabien Hoti
Sponsor project lead	Pål Hasvold	AstraZeneca Nordic Baltic SE-151 85 Södertälje Sweden	19.3.2014	Pål Hasvold

14 Annexes

Annex 1. List of stand alone documents

- Statistical analysis plan
- ENCePP checklist for study protocols.

Annex 2. Variable lists according to data sources

The National Institute for Health and Welfare (THL)

THL will ***identify*** the ***population*** with unstable angina pectoris (ICD-10: I20.0) or myocardial infarction (ICD-10: I21-I24) between 01 Jan 2009 and 31 Dec 2013 in the HILMO register.

For history and follow-up information (years 2004-2013) THL will deliver the data from the HILMO register about

- all diagnoses (ICD-10 codes and dates)
- interventions with a NCSP code beginning with FN (and dates)
- hospitalization periods (starting and stopping days)

For follow-up (years 2009-2013) the data from the Social HILMO register about

- institutionalizations (starting and stopping days)

The above-mentioned data should include the information about the patient (SID codes created by THL, age and sex) and the hospital.

THL converts the patient IDs to SIDs and sends the ID – SID pairs to other register holders: Social Insurance Institution and Statistics Finland. The data sent to EPID Research will include SIDs only.

The Social Insurance Institution

For the population identified in THL the Social Insurance Institution will deliver the data about

- All drug purchases from years 2008-2013 (including one year history)
    - ATCs
    - Purchase dates
    - VNR numbers
    - Package sizes
    - Number of packages
    - Total amount purchased in defined daily doses
- Special reimbursements from years 2004-2013 (including five years history)
    - Special reimbursement and limited special reimbursement decisions with reimbursement and ICD-10 codes
    - Starting and stopping dates
- Place of domicile if abroad at the end of the years 2009-2013

Data sent to EPID Research will include SIDs only.

Statistics Finland

For the population identified in THL Statistics Finland will deliver the data about deaths:

- Date of death
- Causes of death (all levels)

Data sent to EPID Research will include SIDs only.